

# Efficacy and safety of salmeterol/fluticasone compared with montelukast alone (or add-on therapy to fluticasone) in the treatment of bronchial asthma in children and adolescents: a systematic review and meta-analysis

Xiao-Jian Zhou, Zhen Qin, Jiao Lu, Jian-Guo Hong

Department of Paediatrics, Shanghai General Hospital, Shanghai Jiaotong University, Shanghai 200080, China.

## Abstract

**Background:** Despite the recommendation of inhaled corticosteroids (ICSs) plus long-acting beta 2-agonist (LABA) and leukotriene receptor antagonist (LTRA) or ICS/LTRA as stepwise approaches in asthmatic children, there is a lack of published systematic review comparing the efficacy and safety of the two therapies in children and adolescents aged 4 to 18 years. This study aimed to compare the safety and efficacy of salmeterol/fluticasone (SFC) *vs.* montelukast (MON), or combination of montelukast and fluticasone (MFC) in children and adolescents aged 4 to 18 years with bronchial asthma.

**Methods:** A systematic search was conducted in MEDLINE, EMBASE, the Cochrane Library, China BioMedical Literature Database, Chinese National Knowledge Infrastructure, VIP Database for Chinese Technical Periodical, and Wanfang for randomized controlled trials (RCTs) published from inception to May 24, 2021. Interventions are as follows: SFC *vs.* MON, or combination of MFC, with no limitation of dosage or duration. Primary and secondary outcome measures were as follows: the primary outcome of interest was the risk of asthma exacerbation. Secondary outcomes included risk of hospitalization, pulmonary function, asthma control level, quality of life, and adverse events (AEs). A random-effects ( $I^2 \geq 50\%$ ) or fixed-effects model ( $I^2 < 50\%$ ) was used to calculate pooled effect estimates, comparing the outcomes between the intervention and control groups where feasible.

**Results:** Of the 1006 articles identified, 21 studies met the inclusion criteria with 2643 individuals; two were at low risk of bias. As no primary outcomes were similar after an identical treatment duration in the included studies, meta-analysis could not be performed. However, more studies favored SFC, instead of MON, owing to a lower risk of asthma exacerbation in the SFC group. As for secondary outcome, SFC showed a significant improvement of peak expiratory flow (PEF)%pred after 4 weeks compared with MFC (mean difference [MD]: 5.45; 95% confidence interval [CI]: 1.57–9.34;  $I^2 = 95\%$ ;  $P = 0.006$ ). As for asthma control level, SFC also showed a higher full-controlled level (risk ratio [RR]: 1.51; 95% CI: 1.24–1.85;  $I^2 = 0$ ;  $P < 0.001$ ) and higher childhood asthma control test score after 4 weeks of treatment (MD: 2.30; 95% CI: 1.39–3.21;  $I^2 = 72\%$ ;  $P < 0.001$ ) compared with MFC.

**Conclusions:** SFC may be more effective than MFC for the treatment of asthma in children and adolescents, especially in improving asthma control level. However, there is insufficient evidence to make firm conclusive statements on the use of SFC or MON in children and adolescents aged 4 to 18 years with asthma. Further research is needed, particularly a combination of good-quality long-term prospective studies and well-designed RCTs.

**PROSPERO registration number:** CRD42019133156.

**Keywords:** Bronchial asthma; Fluticasone/salmeterol; Montelukast; Systematic review; Pediatric

## Introduction

Asthma is the most common chronic airway disease in childhood and affects approximately 3.0% of children in China between 0 and 14 years of age.<sup>[1]</sup> Despite the decrease in the percentage of children with acute asthma attacks and the frequency of hospitalizations for asthma attacks over the past 10 years,<sup>[2]</sup> uncontrolled asthma in

the pediatric population still poses a substantial challenge in China.<sup>[3,4]</sup> Poorly controlled childhood asthma continues to be a significant economic burden in China, adversely affecting the quality of life of individual sufferers and their caretakers.

Inhaled corticosteroids (ICSs)-containing controller treatment is crucial, and recommended to be initiated as soon as

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**Correspondence to:** Jian-Guo Hong, Department of Paediatrics, Shanghai General Hospital, Shanghai Jiaotong University, No. 100 Haining Road, Hongkou District, Shanghai, 200080, China  
E-Mail: hongjianguo@hotmail.com

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possible after the diagnosis of asthma both in preschool-children (<6 years) and school-aged children and adolescents ( $\geq 6$  years), according to the 2016 Chinese guidelines.<sup>[5]</sup> However, recommendations in stepwise approaches vary from age to age. ICS plus long-acting beta 2-agonist (ICS/LABA) is only recommended as the preferred stepwise control in children  $\geq 6$  years. Although leukotriene receptor antagonist (LTRA, montelukast [MON]) is less effective than regular ICS, LTRA alone and ICS/LTRA are also recommended as alternative therapies for stepwise approaches among children and adolescents.

Limited data from randomized controlled trials (RCTs) suggested that salmeterol/fluticasone (SFC) might be superior to MON in reducing the risk of asthma exacerbation and improving morning pulmonary function in children and adolescents (6–14 years) with asthma.<sup>[6,7]</sup> However, to our knowledge, there is no published systematic review comparing the efficacy and safety of SFC *vs.* MON or combination of montelukast and fluticasone (MFC) limited to children and adolescents aged 4 to 18 years to firmly support this recommendation. Therefore, the objective of this systematic review was to compare the efficacy and safety of SFC *vs.* MON monotherapy or MFC in children and adolescents aged 4 to 18 years with asthma.

## Methods

### Registration

A priori protocol was developed and registered with PROSPERO (registration number: CRD42019133156). This review was informed by, and reported, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>[8]</sup>

### Search strategy

The following electronic databases were searched: MEDLINE, EMBASE, the Cochrane Library, China BioMedical Literature Database, China Academic Journals Full-text Database, Chinese National Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals, and Wanfang Chinese language bibliographic database. All databases were searched from inception to May 24, 2021 using the keywords “asthma,” “salmeterol/fluticasone,” “montelukast,” and “fluticasone.” The search was limited to humans without limitations of date, time, or document type. The search strategies were developed with the assistance of a medical information specialist and were reported in detail [Supplementary Appendix 1, <http://links.lww.com/CM9/A827>]. Additional searches were manually conducted in relevant systematic reviews from relevant databases.

### Study selection

Two reviewers independently performed the literature screening. After removing duplicate records and initial screening of all remaining references via titles and abstracts, the full texts of the references that appeared

to meet the inclusion criteria were obtained and further screened to finalize the inclusion decision. Any disagreement between the two reviewers over eligibility was resolved through discussion with a third reviewer. A study was included if it met the following criteria: (1) Study design: RCTs; (2) Patients: participants aged 4 to 18 years with diagnosed bronchial asthma (asthma diagnosed by a physician based on the criteria recommended by standard clinical pathway or practice guidelines for childhood asthma in different countries<sup>[5]</sup>; full details of diagnostic criteria are given in Supplementary Appendix 2, <http://links.lww.com/CM9/A827>); and (3) Intervention and Control: Comparing SFC with MON, or SFC with MFC, with no limitation of dosage or duration. Trials were excluded if they: (1) included participants who had an acute episode of asthma and (2) were not written in English or Chinese.

### Outcome measures

The primary outcome was the risk of asthma exacerbation (as defined by the original studies). The secondary outcomes included risk of hospitalization, change of pulmonary function (including peak expiratory flow [PEF], PEF%pred, PEF variability, forced expiratory flow rate in one second [FEV<sub>1</sub>], FEV<sub>1</sub>%pred, and forced expiratory flow [FEF] at 25–75% of forced vital capacity [FEF<sub>25–75%</sub>]), asthma control level (as defined by the original studies, including change of Childhood Asthma Control Test [C-ACT], night-time symptom score, day-time symptom score, asthma control level assessment [defined as full controlled, partial controlled, and uncontrolled], asthma symptom-free days, frequency of reliever use, and asthma control questionnaire [ACQ]), quality of life (measured by Pediatric Asthma Quality of Life Questionnaire [PAQLQ] or Pediatric Asthma Caregiver's Quality of Life Questionnaire [PACQLQ]), and the risk of overall adverse events (AEs).

### Quality assessment

Two reviewers independently assessed the quality of included studies using the Cochrane risk of bias tool,<sup>[9]</sup> which is based on sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Overall, a summarized quality of included studies was made according to the risk of bias level in key domains. Any disagreement between reviewers was settled by an additional reviewer referring to the original article.

### Data extraction and analysis

Two reviewers extracted the data independently according to a standard extraction Excel form including: General study characteristics (including first authors, publication years, study center, and sample size); demographic characteristics (including diagnosis, age, and settings); intervention characteristics (including administration of interventions and controls, and treatment duration); and outcome characteristics (including category and definitions of outcome, and follow-up).

Any disagreement between the two reviewers over eligibility was resolved through discussion with a third reviewer. When information was not available in the original article, efforts were made to contact the authors by e-mail.

### Data analysis

Data were synthesized and analyzed using RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK). Dichotomous outcome results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Continuous scales of measurement were expressed as mean difference (MD) with 95% CI. Heterogeneity was calculated using the  $I^2$  statistic. For  $I^2 \geq 50\%$ , the heterogeneity was classified as important and was interpreted according to the study characteristics. A random-effects ( $I^2 \geq 50\%$ ) or fixed-effects ( $I^2 < 50\%$ ) model was used to calculate pooled effect estimates comparing the outcomes between the intervention and control groups where feasible. Sensitivity analysis on different models was planned on the primary outcome to test the robustness of findings. Unfortunately, owing to insufficient data, not all pre-defined outcomes could be performed in meta-analysis, such as risk of asthma exacerbation, risk of hospitalization, change of PEF, change of FEV<sub>1</sub>, asthma symptom free days, changes of ACQ score, PAQLQ score, and PACQLQ score. Therefore, descriptive synthesis of the aforementioned outcomes was performed instead.

## Results

### Study selection

A total of 1006 records were retrieved [Figure 1]. After duplicate publications were removed, 864 studies were included. After screening, 739 records were excluded by ineligible title and abstract. A total of 98 studies with 100 articles were eliminated for other reasons. Thus, 21 studies met inclusion criteria and were retained.<sup>[6,7,10-27]</sup> All trials included childhood and adolescent patients. The age group varied across studies from 4 to 17 years. Seventeen studies reported treatment duration ranging from 8 weeks to 1 year and four studies did not report treatment duration [Supplementary Appendix 2, <http://links.lww.com/CM9/A827>]. All characteristic information was collected based on the reported data from the original studies.

### Characteristics of included studies and patients

A total of 21 RCTs were included with a parallel group design, except for three cross-over designed trials.<sup>[28-30]</sup> There were nine studies comparing SFC with MON<sup>[6,7,11,13-16,23-25]</sup> and 12 studies comparing SFC with MFC.<sup>[10,12,14,17-22,28-30]</sup> These RCTs involved 2643 participants and met the inclusion criteria for this review. Table 1 describes the characteristics of the selected studies [Supplementary Appendix 2, <http://links.lww.com/CM9/A827>].

### Risk of bias in included studies

Quality analysis was conducted based on the aforementioned method and tool. Figure 2 showed the main quality

assessment of studies included. Of the 21 articles included for quality analysis, three studies (14.29%) were of high risk of bias,<sup>[7,16,29]</sup> two studies (9.52%) were of low risk of bias,<sup>[30,31]</sup> and the remaining 16 studies (76.19%) were of unclear risk of bias.<sup>[6,10-15,17-23,25-28]</sup>

### Primary outcome

Two studies reported risk of asthma exacerbation comparing SFC and MON. One showed a significant reduction of the risk of asthma exacerbation in the SFC group after 12 weeks of treatment.<sup>[7]</sup> Another study showed a significant reduction of the risk of emergency entering in SFC group after 1 year of treatment.<sup>[6]</sup> Two studies reported the risk of asthma exacerbation comparing SFC with MFC,<sup>[10,21,22,29]</sup> with no significant reduction [Table 1].<sup>[21]</sup> Sensitivity analysis was not performed because of insufficient data on the primary outcome.

### Secondary outcome

#### Risk of hospitalization

Two studies reported the risk of hospitalization comparing SFC and MON<sup>[6,25]</sup> and one study reported the risk of hospitalization comparing SFC and MFC.<sup>[29]</sup> Also, one study favored SFC after 1 year of treatment [Table 2].<sup>[6]</sup>

#### Pulmonary function

Five studies reported pulmonary functions comparing SFC and MON.<sup>[6,7,11,16,25]</sup> One study assessed FEV<sub>1</sub> and morning and evening PEF and favored SFC after 12 weeks of treatment.<sup>[7]</sup> Three studies assessed PEF%pred<sup>[6,16,25]</sup> with one favoring SFC after 48 weeks of treatment.<sup>[25]</sup> Three studies assessed FEV<sub>1</sub>%pred<sup>[6,11,25]</sup> with one favoring SFC after 48 weeks of treatment<sup>[25]</sup> and one favoring MON after 5 months of treatment [Supplementary Appendix 3 Table 1, <http://links.lww.com/CM9/A827>].<sup>[25]</sup>

Eight studies reported pulmonary functions comparing SFC and MFC.<sup>[10,12,17,18,20-22,29]</sup> Among them, seven assessed the outcomes of PEF%pred,<sup>[10,12,17,18,20-22,29]</sup> two assessed the variation of PEF,<sup>[10,21]</sup> two assessed FEV<sub>1</sub>,<sup>[17,20]</sup> four assessed FEV<sub>1</sub>%pred,<sup>[12,18,21,29]</sup> and two assessed FEF<sub>25-75</sub>%.<sup>[18,21]</sup> The SFC group showed a significant improvement of PEF%pred after 4 weeks (MD: 5.45; 95% CI: 1.57–9.34;  $I^2 = 95\%$ ;  $P = 0.006$ ; Figure 3). SFC group also showed significant improvement of FEV<sub>1</sub>%pred and FEF<sub>25-75</sub>% after 4 weeks of treatment [Supplementary Appendix 4, <http://links.lww.com/CM9/A827>]. Other outcomes of pulmonary function are aggregated in Supplementary Appendix 3 Table 2, <http://links.lww.com/CM9/A827>.

#### Changes in asthma control level

Seven studies assessed changes in asthma control level comparing SFC and MON.<sup>[7,11,13-16,25]</sup> Two reported recurrence rate with no significant difference. Two reported clinical effective rate, favoring SFC after 8 weeks

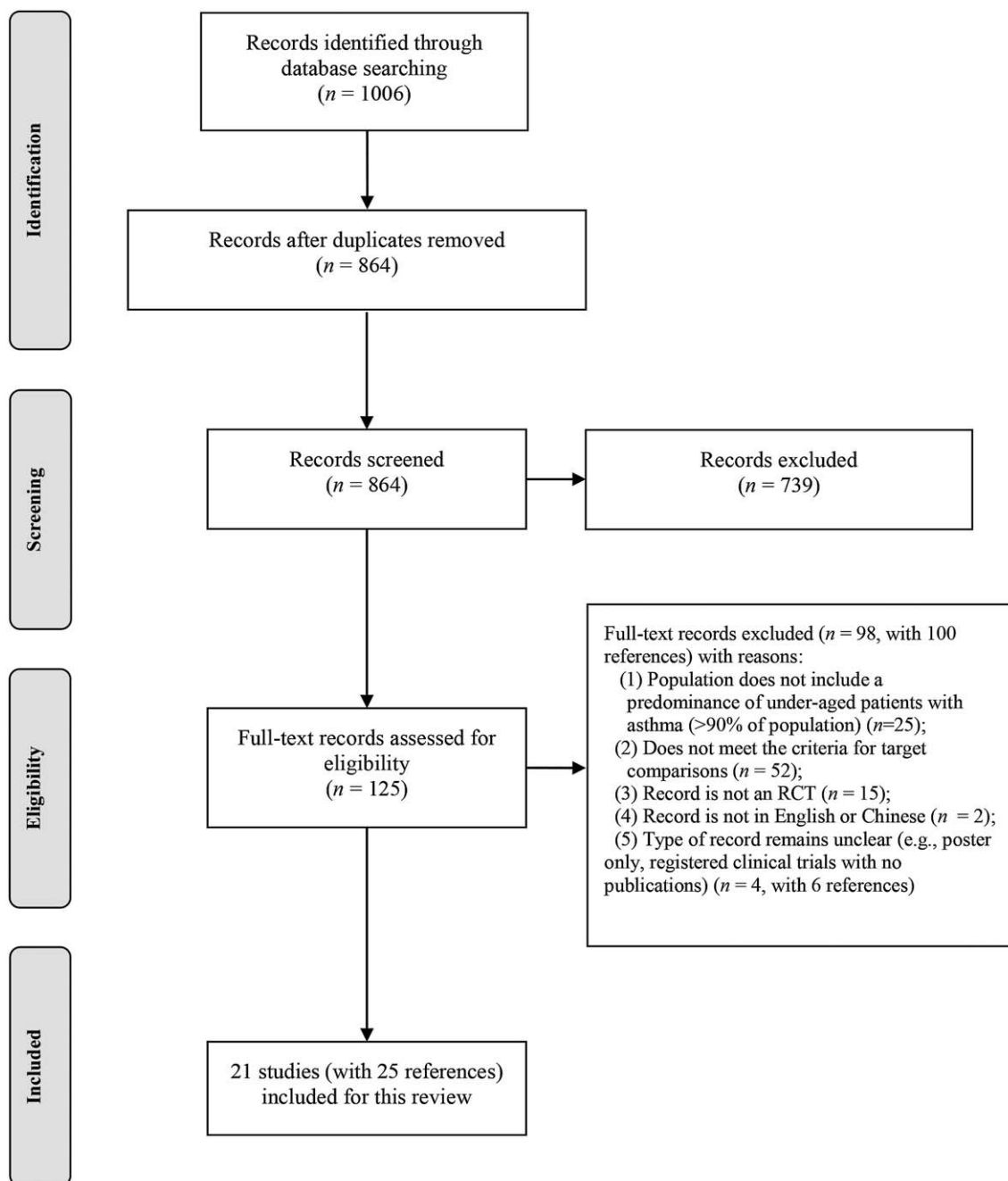


Figure 1: PRISMA study flow diagram. PRISMA: Preferred reporting items for systematic reviews and meta-analyses; RCT: Randomized controlled trial.

of treatment and 5 months of treatment.<sup>[14,15]</sup> Two reported clinical effective rate, favoring SFC after 8 weeks of treatment and 5 months of treatment.<sup>[11,13]</sup> Two reported proportion of asthma symptom-free days, favoring SFC treatment after 12 weeks of treatment and 48 weeks of treatment.<sup>[7,25]</sup> One reported the proportion of patients in complete control<sup>[16]</sup> and the change of ACQ score,<sup>[25]</sup> without significant difference [Supplementary Appendix 5 Table 1, <http://links.lww.com/CM9/A827>].

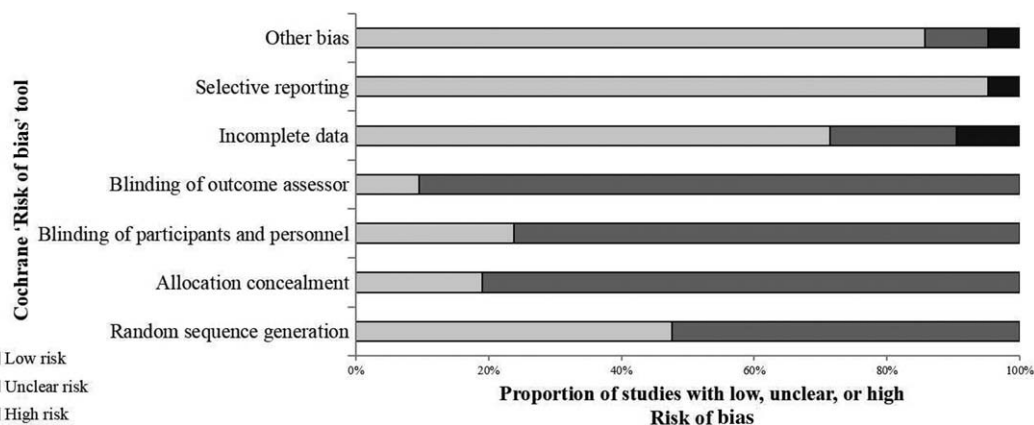
Eight studies assessed changes in asthma control level comparing SFC and MFC<sup>[10,12,17-22]</sup> and all of them reported clinical effective rate. Two assessed day-time and night-time asthma score,<sup>[10,22]</sup> three assessed C-ACT

score,<sup>[12,17,22]</sup> and two assessed the frequency of reliever use.<sup>[10,22]</sup> The SFC group showed significantly higher full controlled level (RR: 1.51; 95% CI: 1.24–1.85;  $I^2 = 0$ ;  $P < 0.001$ ; Supplementary Appendix 6 Figure 1, <http://links.lww.com/CM9/A827>) and lower uncontrolled level (RR: 0.35; 95% CI: 0.24–0.52;  $I^2 = 0$ ;  $P < 0.001$ ; Supplementary Appendix 6 Figure 2, <http://links.lww.com/CM9/A827>), with higher C-ACT score after 4 weeks of treatment (MD: 2.30; 95% CI: 1.39–3.21;  $I^2 = 72\%$ ;  $P < 0.001$ ; Supplementary Appendix 6 Figure 3, <http://links.lww.com/CM9/A827>). SFC group also showed significant improvement in night-time asthma score after 12 weeks of treatment [Supplementary Appendix 6 Figure 4, <http://links.lww.com/CM9/A827>]. Other out-

**Table 1: Summary of primary outcome: risk of exacerbation.**

Study, country	Age, years, mean (range)	Diagnosis	N of Patients	Intervention	Details of treatment	Timepoints of outcomes	Significant key results
Maspero 2008 <sup>[7]</sup> , Latin America and Turkey	9.3 (6–14)	Persistent asthma	548	SFC <i>vs.</i> MON	SFC: Inhaled 50 µg/100 µg BID <i>vs.</i> MON: Oral 5 mg QD for 12 weeks	12 weeks	SFC treatment decreased risk of asthma exacerbation (10.3% <i>vs.</i> 23.2%, <i>P</i> < 0.001)
Ma 2016 <sup>[6]</sup> , China	4.4 (NR)	Mild to moderate asthma	80	SFC <i>vs.</i> MON	SFC: Inhaled 50 µg/100 µg BID (reduced 1/4 dosage for patients' condition and pulmonary functions after 6 months and 12 months) <i>vs.</i> MON: Oral 4 mg (<6 years) or 5 mg (≥6 years) QD for 1 year	6 months, 12 months, and 18 months	SFC treatment significantly decreased the risk of emergency entering at 18 months (7.5% <i>vs.</i> 17.5%, <i>P</i> < 0.05). No significant differences of mild asthma exacerbation at any time
Zhang 2009 <sup>[21]</sup> , China	8.6 (6–13)	Moderate persistent asthma	75	SFC <i>vs.</i> MFC	SFC: Inhaled 50 µg/100 µg BID <i>vs.</i> MFC: Oral 5 mg QD/125 µg BID for 12 weeks	12 weeks	No significant differences
Lenney 2013 <sup>[29]</sup> , UK	10.39 (6.5–14.67)	Uncontrolled asthma	63	SFC <i>vs.</i> MFC	SFC: Inhaled 50 µg/100 µg BID <i>vs.</i> MFC: Oral 5 mg QD/100 µg BID for 48 weeks	24 weeks and 48 weeks	No significant differences

BID: Twice daily; QD: Once daily; MFC: Montelukast/fluticasone; MON: Montelukast sodium; NA: Not applicable; NR: Not reported; SCF: Combination salmeterol/fluticasone; SFC: Salmeterol/fluticasone.



**Figure 2:** Quality of included studies by Cochrane risk of bias tool.

comes of asthma control level are aggregated in Supplementary Appendix 3 Table 2, <http://links.lww.com/CM9/A827>.

**Quality of life**

Only one study assessed quality of life by PAQLQ with no significant difference between SFC and MON.<sup>[7]</sup> One study

assessed the quality of life by PAQLQ and PACQLQ, and the result of PACQLQ favored SFC [Supplementary Appendix 7, <http://links.lww.com/CM9/A827>].<sup>[29]</sup>

**Adverse events**

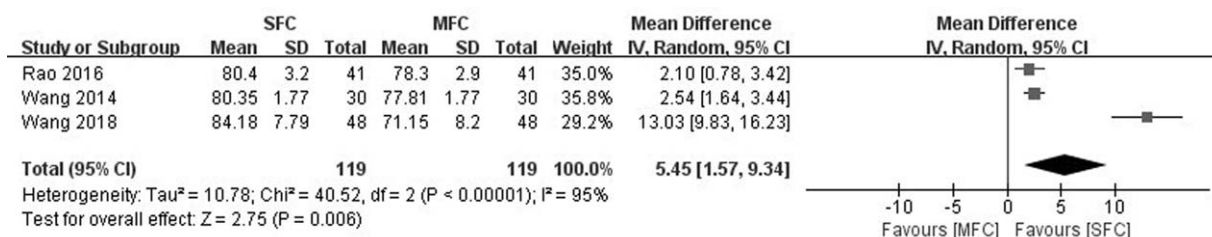
Two studies reported AEs comparing SFC and MON,<sup>[6,7]</sup> both with no significant differences [Supplementary



**Table 2: Summary of secondary outcome: risk of hospitalization.**

Study, country	Age, years, mean (range)	Diagnosis	N of Patients	Intervention	Details of treatment	Timeframe of outcomes	Significant key results
Lenney 2013 <sup>[29]</sup> , UK	10.39 (6.5–14.67)	Uncontrolled asthma	63	SFC vs. MFC	SFC: Inhaled 50 µg/100 µg BID vs. MFC: Oral 5 mg QD/100 µg BID for 48 weeks	24 weeks and 48 weeks	No significant differences
Sorkness 2007 <sup>[25]</sup> , USA	10 (6–14)	Mild to moderate persistent asthma	189	SFC vs. MON	SFC: Inhaled 50 µg/100 µg BID vs. MON: Oral 5 mg QD for 48 weeks	48 weeks	No significant differences
Ma 2016 <sup>[6]</sup> , China	4.4 (NR)	Mild to moderate asthma	80	SFC vs. MON	SFC: Inhaled 50 µg/100 µg BID (reduced 1/4 dosage for patients' condition and pulmonary functions after 6 months and 12 months) vs. MON: Oral 4 mg (<6 years) or 5 mg (≥6 years) QD for 1 year	6 months, 12 months, and 18 months	SFC treatment significantly decreased the risk of hospitalization at 18 months (5% vs. 12.5%, <i>P</i> < 0.001)

BID: Twice daily, QD: Once daily; MFC: Montelukast/fluticasone; MON: Montelukast sodium; NR: Not reported; SCF: Combination salmeterol/fluticasone; SFC: Salmeterol/fluticasone.



**Figure 3:** Results of PEF%pred after 4 weeks of SFC vs. MFC. CI: Confidence interval; MFC: Montelukast and fluticasone; PEF: Peak expiratory flow; SD: Standard deviation; SFC: salmeterol/fluticasone.

Appendix 8 Table 1, <http://links.lww.com/CM9/A827>. Six studies reported AEs with no differences [Supplementary Appendix 9, <http://links.lww.com/CM9/A827>, Appendix 8 Table 2, <http://links.lww.com/CM9/A827>].<sup>[10,17-19,22]</sup>

**Discussion**

Nowadays, there is a lack of evidence on the efficacy and safety of LABAs in the pediatric population which results in unlicensed use of LABA in children aged <4 years for salmeterol and 6 years for formoterol.<sup>[32]</sup> Although LTRAs are less effective than ICS, particularly for exacerbation reduction, they are still recommended as other asthma controllers in children and adolescents.<sup>[33]</sup> In addition, the lack of consensus among domestic and international guidelines regarding ICS/LABA and LTRA treatment options in the pediatric population has led to considerable confusion in China regarding the role of LTRAs for managing childhood asthma in clinical practice. For example, in the Japanese guidelines for childhood asthma (2017), LTRAs can be considered as additional initial therapy as well as a component of graduated step-up treatment options for children and adolescents aged 2 to

15 years<sup>[34]</sup>; similar recommendations have been put forth in the Global Initiative for Asthma (GINA-2019) for children aged 6 years and older (Global Strategy for Asthma Management and Prevention [2019Update]).<sup>[35]</sup> Although in the Chinese guidelines for childhood asthma (2016), ICS/LABA is recommended as the preferred steps 3–5 controller only in children ≥6 years with a suboptimal response to initial ICS treatment. For children <6 years with a suboptimal response to ICS, ICS/LTRA is recommended in step 4.<sup>[36]</sup> LTRA alone and ICS/LTRA are also recommended as an alternative therapy for stepwise approaches for children and adolescents.

This review was undertaken to explore whether a clear benefit exists for either treatment, given the lack of large-scale head-to-head studies. Although it was not possible to perform a meta-analysis of predefined primary outcomes in the 21 RCTs of children and adolescents aged 4 to 18 years with asthma comparing SFC with MON, more evidence favored SFC, which indicated the lower risk of asthma exacerbation of SFC, with an overall reduction rate of 12.9% and 10% after 12 weeks and 1 year of treatment, respectively.<sup>[6,7]</sup> But when compared with MFC, only one study reported the risk of asthma exacerbation and there

were no significant differences between the two groups, which indicated the evidence was still insufficient to make a firm conclusive statement.<sup>[21]</sup>

As for secondary outcomes, there was no difference of risk of hospitalization between SFC and MON. However, more studies favored SFC, with higher asthma control level (four in seven). Comparing SFC with MFC, one study (one in two) favored SFC with a significantly lower risk of hospitalization after 1 year of treatment.<sup>[6]</sup> SFC also showed a significant improvement of pulmonary function (PEF%pred, MD: 5.45; 95% CI: 1.57–9.34;  $I^2 = 95\%$ ;  $P = 0.006$ ), a higher full asthma controlled level (RR: 1.51; 95% CI: 1.24–1.85;  $I^2 = 0$ ;  $P < 0.001$ ), and a higher C-ACT score (MD: 2.30; 95% CI: 1.39–3.21;  $I^2 = 72\%$ ;  $P < 0.001$ ) compared with MFC after 4 weeks of treatment. However, there were no significant differences in most of the pre-defined outcomes after 12 weeks treatment. Meta-analysis could not be performed in other timepoints.

### Strengths and limitations

There are several limitations that warrant consideration. First, the external validity of the studies was quite poor, primarily because of the variability in asthma diagnoses (such as the degree of severity) and the design of RCT. Second, research protocols were not always well described, which resulted in the low quality of evidence. Third, some authors were unable to be contacted. As such, there were some missing details for certain studies, which limited our ability to interpret the data. Finally, in some outcomes, especially when comparing SFC therapy with MFC therapy, most included studies (71.4%) were conducted in the Chinese population, limiting the applicability of the findings worldwide. Despite these limitations, this review has a number of important strengths. First, to our knowledge, no previous systematic review specifically explore the safety and efficacy of SFC compared with MON or MFC of bronchial asthma in children and adolescents aged 4 to 18 years. Second, this review included 15 RCTs with Chinese patients, which would likely improve the implementation of results in Chinese populations.

### Conclusions

Existing evidence suggested that SFC may be more effective than MFC for the treatment of asthma in children and adolescents aged between 4 and 18 years with asthma. But there was still a lack of sufficient evidence to produce a conclusive statement on the optimal choice of SFC or MON. Larger multicenter and high-quality RCTs are required to verify this conclusion and to explore the applicable population, depending on different age, stages, and severity of asthma, and the level of EOS of SFC.

### Conflicts of interest

This work was supported by GlaxoSmithKline (GSK), China. The company did not participant in data screening, extraction and analysis.

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